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Braegger, C P

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Probiotics and the Prevention of Necrotizing Enterocolitis

Christian P. Braegger

Division of Gastroenterology and Nutrition, University Children's Hospital, Zürich, Switzerland

Necrotizing enterocolitis is one of the most serious gastrointestinal emergencies in the neonatal intensive-care unit [1]. It predominantly affects preterm infants. The onset of disease is usually between the 3rd and the 10th day of life. Necrotizing enterocolitis presents with a wide spectrum of clinical symptoms, ranging from non-specific gastrointestinal disturbance to a fulminant course of intestinal gangrene and perforation. Typical early signs are abdominal distension, delayed gastric emptying, diarrhea, abdominal tenderness and gastrointestinal bleeding. Characteristically, extensive hemorrhagic inflammatory necrosis of the terminal ileum and ascending colon can be found. In severe cases the entire bowel may be involved. Intramural hemorrhage, gangrene, peritonitis and edema may progress to intestinal necrosis with extensive infiltration of neutrophil leukocytes.

Risk factors include prematurity, hypoxia, formula feeding, bacterial infection and intestinal ischemia [2, 3]. Mortality is high (15–30%) and related to the presence of bacteremia, disseminated intravascular coagulation, ascites and very low birth weight. Etiology and pathogenesis of necrotizing enterocolitis remain unknown. However, formula feeding, intestinal mucosal barrier dysfunction and dysbalance of bacterial colonization may be contributing factors, leading to an inappropriate inflam-

matory response of the immature intestinal immune system, resulting in rapidly evolving intestinal gangrene, perforation, sepsis, shock and death [1, 2, 4].

Probiotics have been shown to be able to modify both the intestinal microbiota as well as the intestinal immune response. On this background, several clinical trials have been carried out in order to investigate the potential role of probiotics in the prevention of necrotizing enterocolitis [5–13]. Most of these studies, among them many randomized controlled trials, suggest a significant benefit of probiotics in the prevention of necrotizing enterocolitis, confirming previous observations in experimental animal models [14, 15]. Possible mechanisms of probiotics in the prevention of necrotizing enterocolitis are beneficial modification of the intestinal microbiota, strengthening of the intestinal mucosal barrier and attenuating the intestinal immune response to bacteria and bacterial products.

The results of the randomized controlled trials have been analyzed in several comments and reviews [16–19]. There is a general agreement that probiotic supplementation has a great potential to significantly reduce the risk of necrotizing enterocolitis and the overall mortality in premature infants with very low birth weight. However, there is obviously great variability of the clinical trials reported, with respect to inclusion criteria of the patients,

type and dose of probiotics used, duration of treatment and feeding regimens.

A further concern is safety. Although sepsis caused by probiotics was not observed in any of the randomized controlled trials on the prevention of necrotizing enterocolitis, there are rare case reports of systemic infections caused by probiotic bacteria in children with underlying diseases [20–23]. The long-term safety of probiotic bacteria in terms of permanent alteration in the intestinal bacterial colonization should also be studied.

In conclusion, probiotics appear to be safe and effective in preventing necrotizing enterocolitis in very low birth weight infants. There is increasing evidence that supplementation with probiotics may reduce both the risk of necrotizing enterocolitis as well as mortality in

preterm infants. However, there is great heterogeneity among the published clinical trials and therefore insufficient information to make sound recommendations for the type of organism, dose and timing that should be used for probiotic supplementation in very low birth weight infants. Therefore, further large well-designed multicenter trials are urgently needed before the use of probiotics in preterm infants may become routine in all neonatal intensive-care units.

Disclosure Statement

C.P.B. has been an advisory board member for Danone.

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